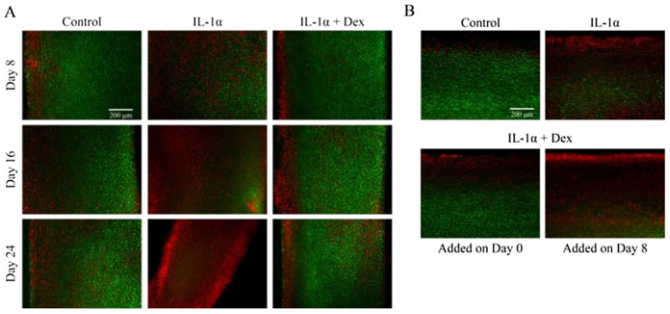
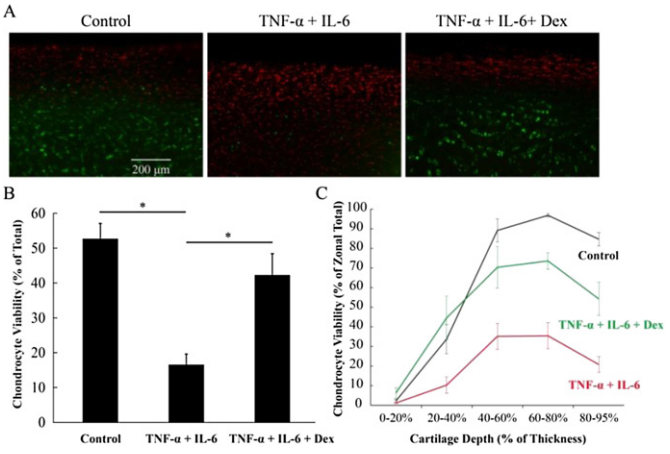
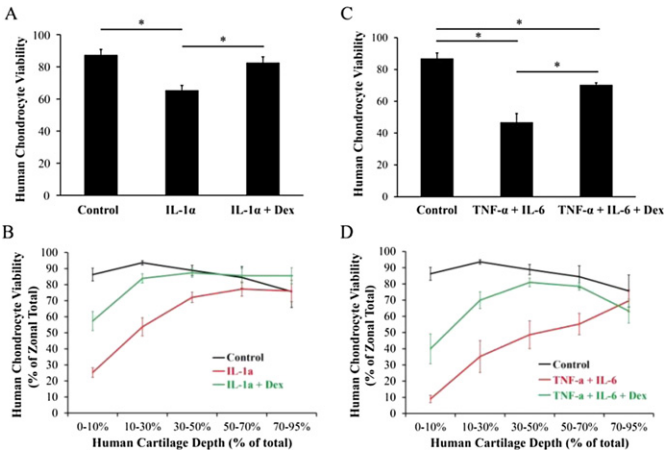
(100 nM), TNF-α (25 ng/ml), IL-6 (50 ng/ml), and soluble IL-6 receptor (sIL-6R, 250 ng/ml). In Study 1A, bovine disks (N = 6 per group and time point) were incubated with IL-1α with or without Dex for a period of 8, 16 or 24 days. In Study 1B, bovine disks (N = 6 per group) were incubated with IL-1α for the first 8 days, and then switched to cytokine-free medium for another 8 days; Dex treatment started on either Day 0 or Day 8, and continued until Day 16. In Study 2, human knee disks (N = 9 per group) were treated with the combination of TNF-α, IL-6, and sIL-6R with or without Dex for 17 days. In Study 3, human ankle disks (N = 6 per group) were incubated either with IL-1α or the combination of TNF-α, IL-6, and sIL-6R with or without Dex for 17 days. Disks were stained with Fluorescein Diacetate (green, for viable cells) and Propidium Iodide (red, for non-viable cells). Cell viability was quantified using ImageJ: images of each disk were divided into 5 zones for evaluation (except the deepest 5% which had low viability due to cutting-induced cell death). Data are mean ± SEM. Statistics: 2-way ANOVA with Tukey post-hoc test, * $p<0.05$.

Results: Representative images showed that Study1A bovine cartilage treated with IL-1α displayed significant cell death compared to untreated controls as early as 8 days after treatment (Fig 1A). The addition of Dex, however, completely reversed the detrimental effect of IL-1α on chondrocyte viability, and this rescuing effect was sustained over 24 days. In Study 1B, Dex successfully rescued IL-1α-induced cell death when it was introduced on Day 0 (Fig 1B, bottom left), but no rescuing effect was observed when added on Day 8 (Fig 1B, bottom right). In Study 2, TNF-α/IL-6 treatment caused significant cell death in the normal human knee disks, and this was prevented to a large extend by Dex (Fig 2A&B). In Study 3, IL-1α and TNF-α/IL-6 both induced significant cell death in the human OA ankle disks, which were rescued by Dex (Fig 3A&C). Depth-dependent cell viability showed that the anti-apoptotic effect of Dex was present throughout the entire thickness of the tissue (Fig 2C,3B&D).

Conclusions: To our knowledge, this is the first report to show ability of dexamethasone to rescue the loss of cell viability in cytokine-treated young bovine (normal), adult human (normal and Collins grade-1) cartilage. However, Dex could not rescue cells that had already undergone terminal cell death. This study strongly supports the idea of using Dex as a potential therapeutic for incipient cell death (e.g., apoptotic) relevant to post-traumatic OA.







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SYNOVITIS IN OA: A PRECURSOR OF DISEASE? THE ONSET OF SYNOVITIS AND RADIOGRAPHIC OSTEOARTHRITIS IN A INCIDENCE SUB COHORT OF THE OSTEOARTHRITIS INITIATIVE (OAI)

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Purpose: Synovitis and joint inflammation are believed to play a role in the pathogenesis of osteoarthritis (OA). However, it is still unknown whether joint inflammation (Hoffa synovitis/effusion-synovitis) precedes the occurrence of radiographic knee OA. Therefore, the aim of this study was to identify if inflammation precedes, and predicts the development of structural damage defined as radiographic knee OA (ROA).

Methods: The participants in this nested case-control study were selected from the Osteoarthritis Initiative (OAI) incidence subcohort. This subcohort contained individuals who; despite having risk factors for OA; did not have ROA in the target knee(or collateral knee) at baseline. Participants were assessed by knee radiographs and non-contrast magnetic resonance imaging (MRI) using the OAI protocol, over a four-year period. The MRIs were assessed for presence and timing of onset of Hoffa synovitis or effusion-synovitis using the MRI Osteoarthritis Knee Score (MOAKS). Cases were individuals who developed ROA during the study defined as Kellgren and Lawrence grade (KLG) of >=2 on the PA view fixed flexion radiographs. The controls (i.e, did not develop incident ROA over the four-year period) were 1-1 matched by age group (within five years), sex, and baseline KL status (i.e., KLG 0 bilaterally at baseline). Survival analysis using discrete-time Cox Proportional Hazards Regression was used to estimate the hazard ratios (HR) of predicting incident ROA. HRs for each key predictor, were modelled at three timepoints: the timepoint concurrent with incident ROA (P0), the timepoint 1 year prior to incident ROA (P1) and baseline.

Results: 63 persons who developed ROA (38 females) were matched to 63 controls (38 females). Mean ages of cases and controls were 58.1 years (SD± 8.58) and 57.8 (SD± 8.58) years, respectively. Mean body mass index was 28.8 (SD± 4.96) in cases and 26.9 (SD ± 4.65) in controls, respectively. 41.2% of cases and 28.6% of controls were obese. HRs for incident ROA based on the presence of effusion-synovitis and Hoffa synovitis at baseline were 5.5 (1.2-24.8) and 2 (0.9-4.5), respectively. The HRs for presence of effusion-synovitis and Hoffa synovitis one year prior to incident ROA (P1) and at point of occurrence of incident ROA (P0) were 7.7 (2.3-25.5) and 3 (1.2-7.6), and 28 (3.8-205.8) and 4 (1.5-10.7), respectively (Table 1).

Conclusions: Effusion-synovitis and Hoffa's synovitis both strongly predicted the development of incident ROA. Joint inflammation appears to play an important role in the development of incident radiographic OA.